Chronic Heliodermatitis: A Morphologic Evaluation of Chronic Actinic Dermal Damage With Emphasis on the Role of Mast Cells

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Descriptions of actinically damaged human dermis have focused on the late stages of elastotic degeneration. This has diverted attention from preceeding events, which are important for understanding the sequence of pathologic changes that culminate in the deranged fibrous structures of elastotic dermis. We studied specimens from the back of the necks (exposed) and inner arms (unexposed) of 24 individuals, aged 35–84 yr, by light and transmission electron microscopy. Intense sunlight exposure was common to all. A previously undescribed finding was the presence of a perivenular, histiocytic–lymphocytic infiltrate in which numerous mast cells, often in close apposition to fibroblasts, were observed. We have termed this "chronic heliodermatitis." We postulate that mast cell-derived mediators in conjunction with enzymes released by the infiltrating cells lead to breakdown of elastic and collagen fibers. *J Invest Dermatol 90:325–330, 1988*

The deleterious effects of solar radiation on human skin have been extensively studied. Sunburn is the acute response to a single high dose of UVB (290–320 nm); its histologic picture is distinctive, showing scattered dyskeratotic "sunburn" cells, inter- and intracellular edema, and eventual necrosis of the superificially located keratinocytes [1,2]. The dermis is surprisingly spared. Inflammatory cells are scanty though hypogranulated mast cells and perivascular edema are often found. By contrast, a single high dose of UVA (320–400 nm) largely spares the epidermis and damages the superficial vessels [3]. An infiltrate of neutrophils surrounds the vessels.

Decades of exposure to solar radiation, especially in light-skinned persons, eventuates in a great variety of visible changes: wrinkling, yellowing, laxity, mottling, scaling, leatheriness, and an assortment of premalignant and malignant neoplasms. The term dermatoheliosis covers all these changes [4]. Histologic and histochemical alterations in the dermis include massive accumulation of abnormal elastic fibers, loss of collagen, increase of glycosaminoglycans (GAGs) and telangiectatic vessels [5,6]. These well known alterations comprise the end-stage of actinic damage when the matrix has been structurally ruined. Ultimately, the fibrous network degenerates into amorphous, elastotic masses [7]. Small vessels become sparse and tortuous [8].

Most histologic studies of dermatoheliosis have dealt with end-stage elastotic degeneration. What has largely been overlooked is the sequence of changes, occuring over decades, which finally bring about the destruction of the matrix. Specimens from grossly elastotic skin are too damaged to reveal preceding events. Though massive hyperplasia of abnormal elastic tissue dominates the histologic picture and has captured most attention, the loss of collagen, has evoked little interest. This alteration of collagen and elastin accounts for the sagging and loss of resilience of badly photodamaged skin.

After studying many specimens of actinically damaged skin from subjects ranging from 20 to 80 yr old, we came to appreciate a slowly evolving pattern of changes in which a perivascular inflammatory infiltrate was a prominent feature. Chronic inflammatory changes in photodamaged skin have not been heretofore described. We have named this "heliodermatitis." This low-grade, chronic inflammation is generally below the level of clinical visibility. Still, physicians who see large numbers of light-skinned persons of Celtic extraction (type I skin) are quite familiar with a persistent erythema, generally of the face and neck, comprising the visible expression of heliodermatitis. A local parlance, these persons are sometimes called "rednecks," a denigrating term for poor, outdoor laborers, obliged to work a lifetime under the sun. In tanned type 3 to 4 individuals, the erythema is concealed, but the inflammatory process is present nonetheless.

We shall not discuss the drastic alterations in actinically damaged epidermis. These have been well described [9].

MATERIALS AND METHODS

We studied 24 individuals with skin type I or II, aged 35–84 yr, having a history of prolonged sunlight exposure. All showed varying degrees of actinic damage, ranging from little more than mottling and wrinkling in the youngest to yellowed, lax skin with many actinic keratoses in the oldest. Three-millimeter punch biopsies were performed on the back of the neck of nine subjects and on the malar eminence of the cheek from the remaining 15. Half of these individuals also underwent a 3-mm biopsy from the unexposed inner arm. Each specimen was fixed in 10% buffered formalin, embedded in paraffin, and sectioned at 6 μm. In addition to hematoxilyn and eosin staining, elastic fibers were visualized with Luna's aldehyde fuchsin, Van Gieson for collagen, reticulin by Gordon and Sweet's silver stain, and Mowry's collodial iron for glycosaminoglycans (GAGs).

In 13 subjects, the tissue was processed for transmission electron microscopy as previously described [10]. Briefly, they were immediately fixed by immersion in 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate–HCl, buffered (pH 7.4) for 2 h at

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24°C. Postfixation was for 1 h in 1% osmium tetroxide. After dehydration through a graded series of alcohols, the specimens were embedded in Epon 812. Thin sections were cut with a diamond knife on a Porter–Blum MT-2B microtome, stained with saturated uranyl acetate and lead citrate and examined in a Hitachi HU-12A electron microscope. One-micron sections for light microscopy were prepared from the same Epon-embedded specimens. These were stained with toludine blue and counterstained with basic fuchsin [10].

RESULTS

We used the degree of elastosis as a marker of the intensity of actinic damage. Early on, before any other changes, there was a simple increase in the quantity of apparently normal, fine branching elastic fibers (Fig 1*a*). Later the fibers became thicker, twisted, curled, and highly branched, often appearing as short segments (Fig 1*b*). The middermis accumulated large amounts of abnormal elastotic material (Fig 1*b*). In severe actinic damage, elastotic material replaced most of the upper dermis, except for the thin subepidermal Grenz zone (Fig 1*c*). In the final stage, the tangled mass of fibers degenerated into nodular masses of amorphous material in which remnants of elastic fibers could barely be made out (Fig 2*a*). There were virtually no vessels within these structureless foci sequestered between follicles, nor could collagen bundles be found by Van Gieson's stain. These structureless accretions account for the yellow-pebbly appearance of advanced photodamage.

In moderate elastosis, the microvasculature was more sparse and irregular. A conspicuous finding by serial sectioning was perpendicularly oriented, widened venules, recognized by their thick walls

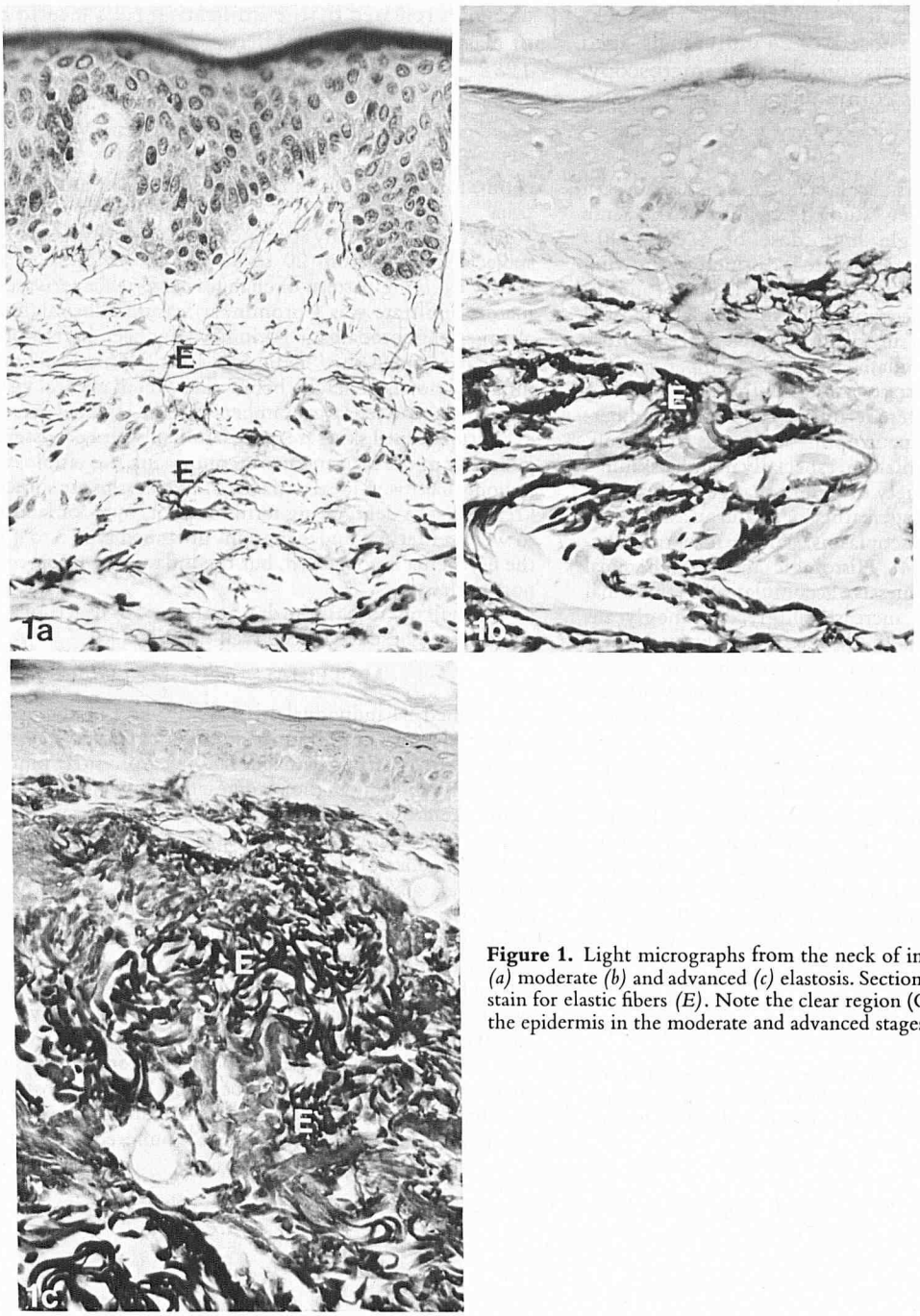

Figure 1. Light micrographs from the neck of individuals showing early *(a)* moderate *(b)* and advanced *(c)* elastosis. Sections are stained with Luna's stain for elastic fibers *(E)*. Note the clear region (Grenz zone) just beneath the epidermis in the moderate and advanced stages of elastosis (×200).

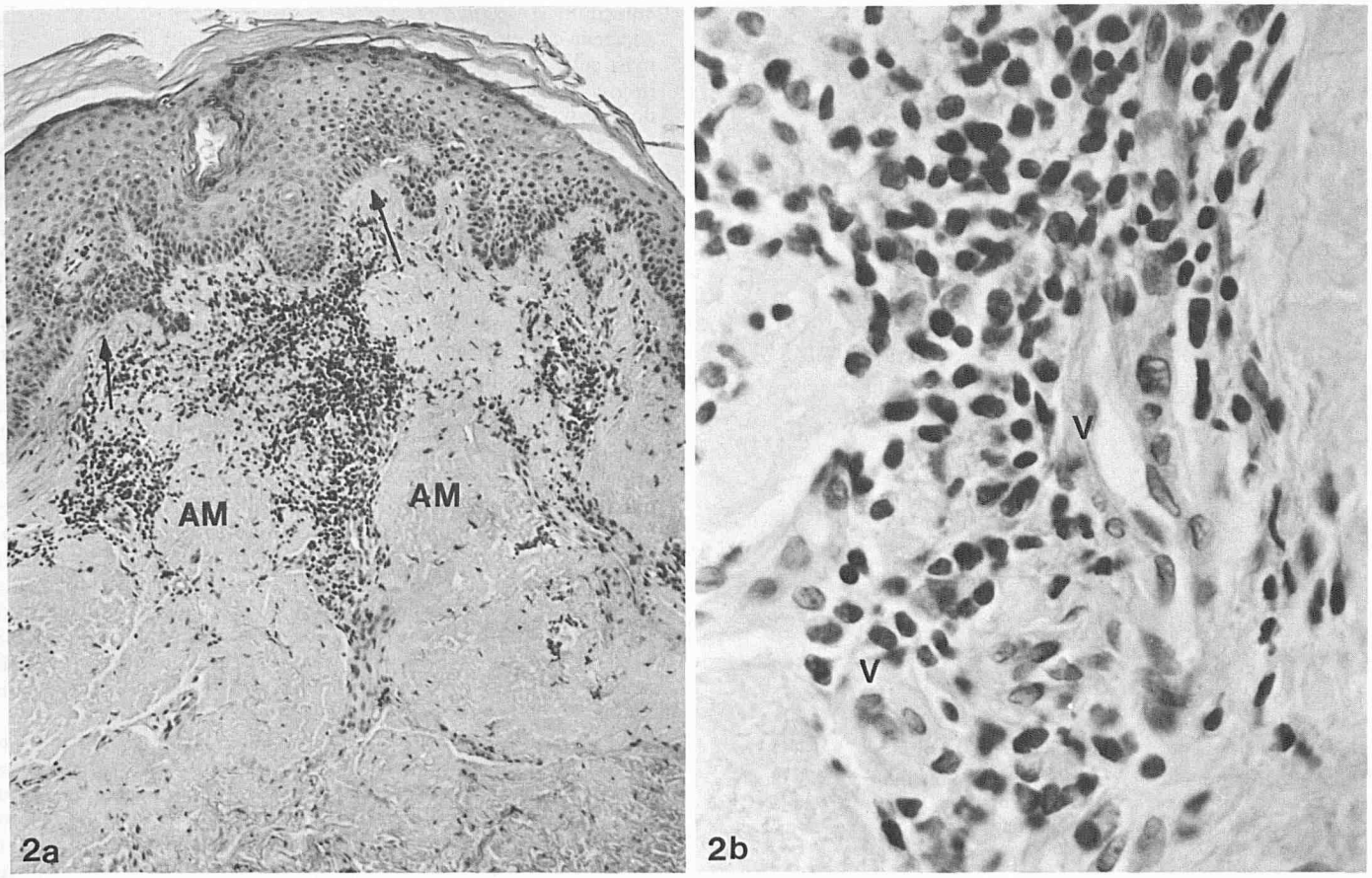

Figure 2. *(a)* Light micrograph from a sun-damaged neck showing a persistent erythema. Mononuclear infiltrate surrounds nodular masses of amorphous material *(AM)*. Note lack of vessels within the nodular masses of elastotic amorphous material. Grenz zone *(arrows)* separates the elastotic tissue from the epidermis *(E)* (×250). *(b)* Light micrograph showing the perivenular *(V)* lymphohistiocytic infiltrate characteristic of persons with moderate actinic damage (×400).

(Figs 2*a*, 2*b*). These dilated venules were surrounded by a distinctive infiltrate of inflammatory cells consisting mainly of lymphocytes, a moderate number of histiocytes, and numerous mast cells (Fig 2*b* and Fig 3). The infiltrate was segmental and not uniformly distributed along the vessel wall. The same mixed infiltrate was often located around sebaceous glands, probably in relation to the enveloping vasculature. Perivenular infiltrates were generally not found in the end-stage amorphous nodules, which mainly showed markedly telangiectactic, sparse venules.

Inflamed venules were surrounded by increased amounts of multiple laminations of basement membranelike material with a normal compliment of pericytes (Fig 4). The endothelial cells of the involved vessels appeared swollen, but were otherwise normal. We did not observe necrosis of the vessel wall, fibrin depostion, neutrophils, nuclear karyorrhexis, or extravasation of red blood cells (Figs 2*b* and 4). We noticed these perivenular inflitrates only by serial sectioning, owing to the sparsity of vessels. In late stage degeneration, they were altogether absent within the nodules but could be identified around the periphery.

Numerous mast cells, exhibiting varying degrees of degranulation were an invariant feature of the actinically damaged dermis observed in each of the 13 subjects studied with the transmission electron microscope (Fig 3, and Fig 4). Adjacent mast cell granules were often fused, forming masses of flocculent material. Gaps in the mast cell membrane and exocytosis of granules were regularly observed. In some instances, free mast cell granules were observed adjacent to the elastotic material.

A unique aspect of the mast cells in chronic heliodermatitis was their frequent contacts with fibroblasts (Figs 3 and 4). Examination of serial sections showed a network of specialized membrane appositions between fibroblasts and mast cells. Occasionally, fibroblasts were observed with a pseudopod making contact with a neighboring mast cell (Fig 4). The pseudopod was filled with microfilament bundles aligned parallel to the extension. The tip of the pseudopod showed villus projections, which appeared to intertwine with the mast cell microvilli. Exocytosis of mast cell granules was often evident at this junction (Fig 4).

A classic feature of actinically damaged dermis is the Grenz zone, which seems to escape injury. It appears as an eosinophilic subepidermal homogeneous band, sharply demarcated from the elastotic material below (Figs 1*c*, and 2*a*). This band stained positively for reticulin, indicating newly formed collagen. By electron microscopy the Grenz zone consisted of horizontally distributed bundles of normal collagen fibers. Elastic fibers were absent (Fig 5).

Beneath the Grenz zone, there was a disorderly conglomeration of collagen bundles and elastotic material. Although collagen bundles were sparse in densely elastotic tissue, individual fibers were apparently normal. We did not observe degenerating fibers (Fig. 6).

In severe elastosis there was a network of fine fibrillar material with a periodic banding pattern of 1000 A. These were typical "zebra bodies" and were interspersed with residual collagen fibers, usually in the vicinity of fibroblasts (Fig 7).

The elastotic material in advanced cases took different forms. Just beneath the Grenz zone (Fig 5, and Fig 6), there were swollen, almost completely degenerated elastic fibers containing irregular masses of electron dense material, probably aggregations of

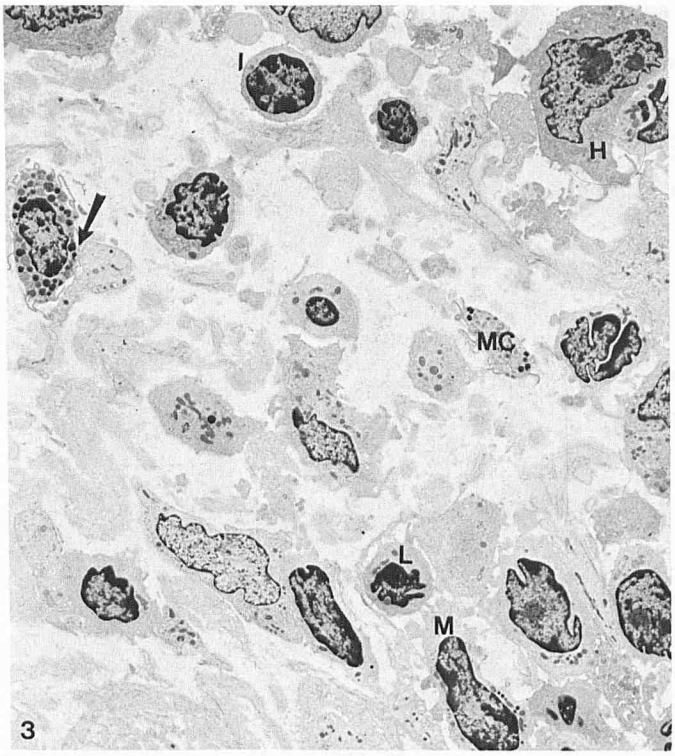

Figure 3. Electron micrograph of a protion of the infiltrate showing lymphocytes *(L)*, histiocytes *(H)*, and macrophages *(M)*. Mast cells *(MC)* in varying stages of degranulation are abundant. Note close apposition of a mast cell with a fibroblast *(arrow)* (×2000).

clumped microfibrils. Below this zone of advanced degeneration there were many swollen elastotic fibers with electron-lucent, irregularly sized cavities (Fig 6). More deeply situated, but less damaged elastic fibers showed the same cavities.

DISCUSSION

A constant, heretofore undescribed feature of solar elastosis, noted in all individuals studied, and occurring before the stage of complete amorphous degeneration, was a perivenular, segmental, histolymphocytic infiltration with an admixture of degranulating mast cells. Past investigations mainly studied end-stage elastosis in which there is a drastic deletion of vessels. In midstage heliodermatitis, the vessel walls were thickened because of a large deposition of basement membranelike material. This was previously noted by Braverman and Fonferko [8] in actinically damaged skin. They proposed that veil cells, which are probably modified fibroblasts, were stimulated by ultraviolet radiation to produce excessive amounts of the basement membranelike material. We, too, think that exuberant production of basement membranelike material is a reparative response to persistent injury, analagous to the reduplication of lamina densa after various chemical and physical epidermal injuries [6,11]. It may be a marker of vascular repair. The endothelium of these vessels seemed perfectly normal, probably reflecting continuous renewal.

The occurence of numerous mast cells in heliodermatitis is consistent with findings of increased mast cells at sites of chronic inflammation [12–15]. It should be noted that increased numbers of mast cells are not a common feature of protected skin of the aged, but are often noted in sun-aged skin [6,7]. The observation of fibroblasts extending pseudopods towards, and intertwining with mast cell microvilli, sometimes with cell-to-cell fusion, provides the first evidence of intimate contact between mast cells and fibroblasts in human skin. Furthermore, mast cell degranulation, at the site of the fibroblast–mast cell apposition, might mediate biochemical communication between these two cell types. This form of cell-to-cell communication involving secretion of mast cell products to other adjacent cell types has been previously observed in co-cultures of mast cells and fibroblasts [16]. A similar interaction was also noted in vivo in rat mesentery [16]. In contrast to our findings, the pseudopods were formed by mast cells that then attached to the surface of opposing fibroblasts. Fibroplasia resulting from the secretion of mast cell constituents into adjacent fibroblasts has been suggested as a potential role of mast cells in chronic inflammation [17]. The fibroblast, mast cell interactions described in the present study supports this notion. In the early stage of heliodermatitis, we have preliminary evidence of increased deposition of collagen (Grenz zone). It is noteworthy that the organization of the Grenz zone is similar to the architecture observed in healing wounds [6,18,19]. This is a zone of new collagen formation, evidenced by an abundance of reticulin, signifying an ongoing process of repair.

The presence of numerous degranulating mast cells indicates that a variety of mediators and chemotactic factors are being liberated into the extracellular space. A partial listing of these include histamine, arylsulfatase A, slow-reacting substances (leukotrienes), prostaglandins, and a variety of proteases [20]. Human skin mast cells have been shown to contain two serine proteases having trypsinlike and chymotrypsinlike activity [21]. The chymotrypsinlike enzyme affected only the lamina lucida, lamina densa, and subepidermal elastin microfilaments when incubated with normal human dermis [22]. However, the elastic fibers in elastotic skin are grossly abnormal, and therefore might be unusually susceptible to proteolysis. In any case, both elastin and collagen fibers are markedly decreased in the papillary dermis in end-stage sun-damage.

The mediators liberated by mast cells doubtlessly contribute to the chronic inflammatory reaction. Additionally, macrophages, abundant in the infiltrate, are capable of secreting elastase, and other enzymes, including collagenase [23]. These proteinases likely contribute to the breakdown of the elastic and collagen fibrous network. Then, too, fibroblasts, which are large and abundant in the early stages of ultraviolet injury [24], also secrete collagenase. The origin of zebra bodies is controversial. They could either be a type of newly synthesized collagen or a breakdown product [3]. They have also been found after long-term PUVA therapy [25]. They are, therefore, not a specific marker of ultraviolet radiation damage.

It must be emphasized that in vitro irradiation of human skin does not lead to destruction of collagen or elastin, no matter what the dosage (unpublished observations). Thus, the dissolution of elastic fibers occurs indirectly, though photons might physically alter elastin to some extent. It should be noted that neutrophils are typically absent in chronic heliodermatitis, though they are a potent source of elastase [26].

The process of actinic dermal damage begins with increased formation of thickened, tangles of abnormal elastic fibers in which microfilaments clump together in aggregates [6]. Elastogenesis is the hallmark of this first stage. Later, elastolysis becomes evident, with a moth-eaten appearance due to numerous cavities that evidently result from dissolution of the elastin matrix [7]. Finally, dense aggregates of microfilaments form within swollen, degenerated fibers. This takes place against a background of microfibrillary material, in which zebra bodies are found, interspersed with scanty collagen fibers. This fibrillary background is the end-stage of degeneration, appearing as a dark amorphous mass in the light microscope.

In the final stage there is massive dissolution of elastic fibers accompanied by a loss of collagen. It is clear that these changes evolve over a period of many years, starting as early as the second decade [5] and, depending on skin type and exposure, ending in virtual disorganization of the matrix 20–40 yr later. We believe that the mast cell as well as the perivenular infiltrate play a decisive role in this progression.

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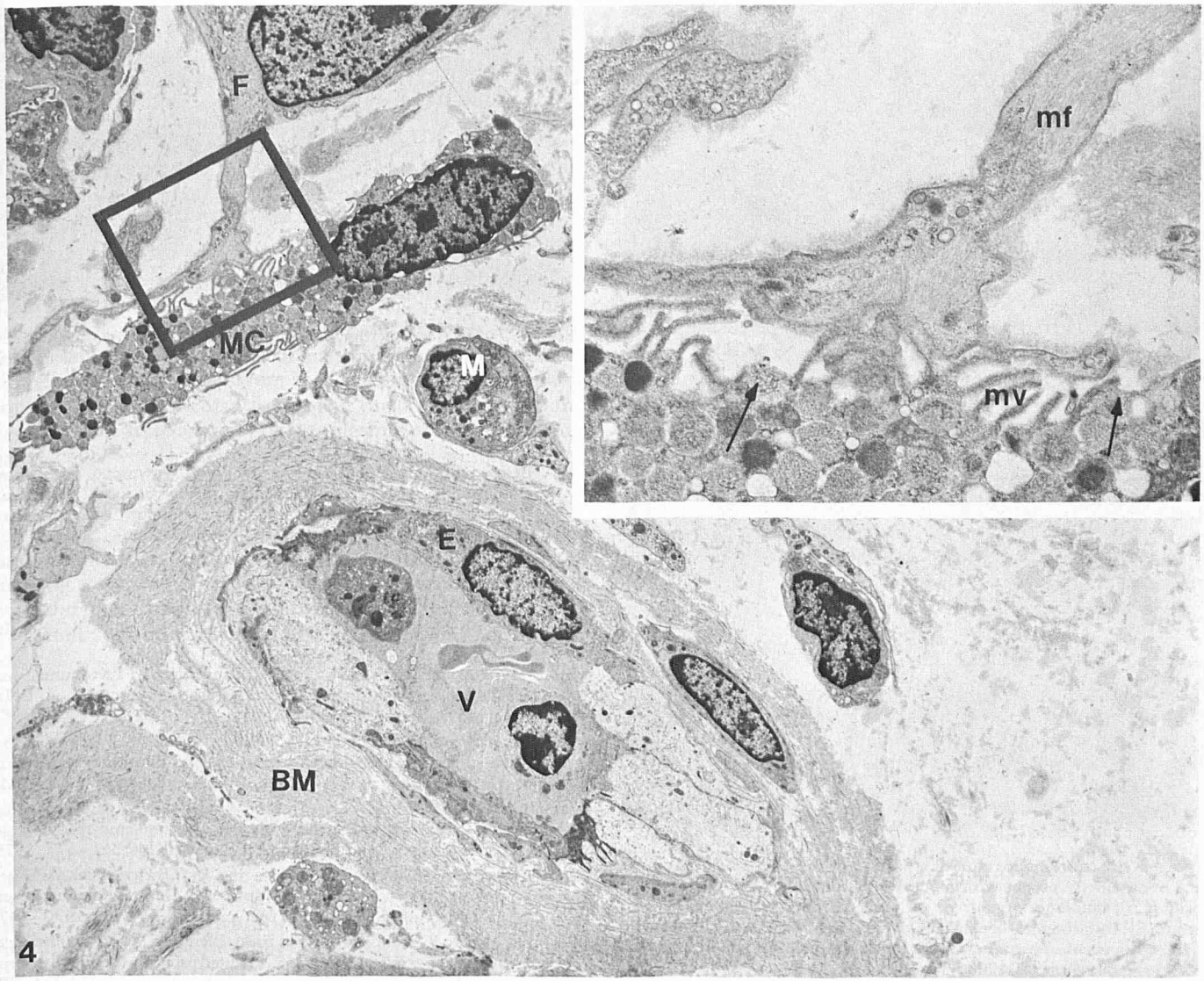

Figure 4. Electron micrograph of a dilated venule *(V)* surrounded by multiple laminations of basement membranelike material *(BM)*. Fibroblast *(F)*, with a pseudopod extension is in contact with a degranulating mast cell *(MC)*. *E*, endothelial cell: *M*, macrophage (×3500). *Inset:* High magnification of area in rectangle showing fibroblast pseudopod filled with microfilament bundles *(mf)* intertwining with mast cell microvilli *(mv)*. Fusion of mast cell granules and exocytosis of their contents is evident *(arrows)* (×12000).

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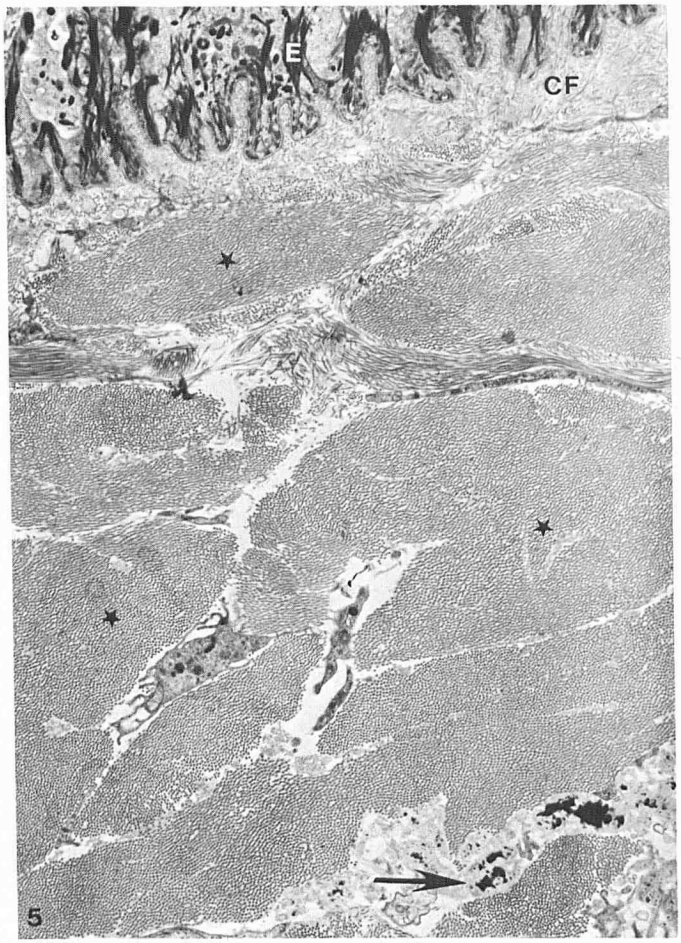

Figure 5. Electron micrograph of a portion of the Grenz zone from the neck of an elderly person with moderate actinic damage. Single collagen fibrils *(CF)*, randomly organized, are observed directly beneath the epidermis *(E)*. Large bundles of collagen *(asterisk)* organized parallel to the skin surface comprise the remaining Grenz zone. Note elastotic material beneath the Grenz zone *(arrow)* (×2000).

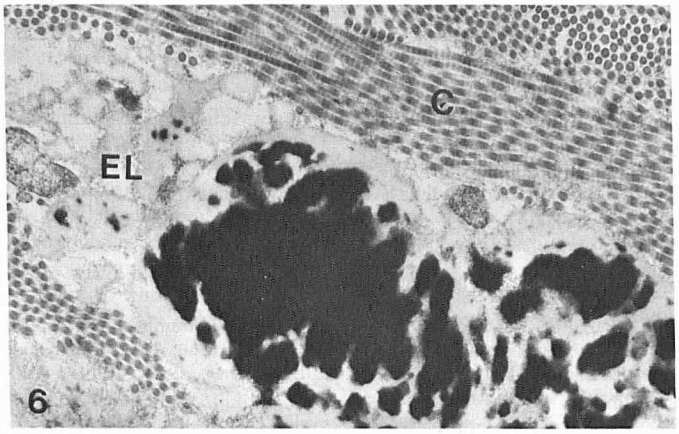

Figure 6. Electron micrograph of elastotic material showing degenerated elastotic fibers with masses of irregular electron dense material. Electron lucent *(EL)* regions give a "moth-eaten" appearance. Collagen fibrils *(C)* appear normal (×18000).

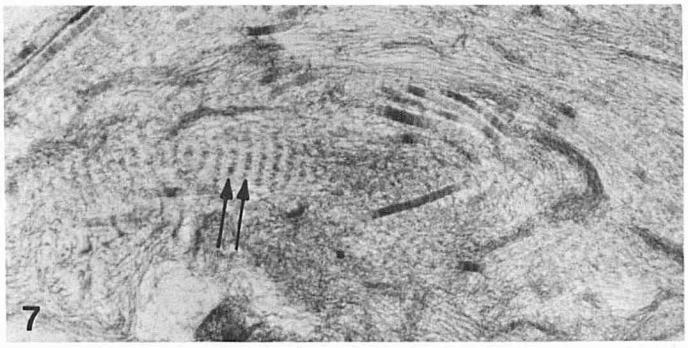

Figure 7. Electron micrograph showing aggregations of fine filaments with a periodic banding pattern of 1000 A *(arrows)* characteristic of "zebra bodies" (×20000).

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